Efficacy of Azacitidine in de Novo and relapsed acute Myeloid Leukemia: A retrospective comparative study

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Abstract: Introduction: Azacitidine is a therapeutic alternative to low-dose cytarabine in patients with acute myeloid leukemia (AML) who are unfit for intensive chemotherapy. Patients and Methods: We retrospectively analyzed all AML patients treated with azacitidine at the University Hospital Zurich and the Kantonsspital Munsterlingen between January 2005 and December 2011. The primary end point was overall survival (OS). Results: Thirty-eight patients were included in the analysis. Twenty-one (55%) patients had newly diagnosed AML, 14 (37%) had relapsed AML, and 3 (8%) underwent bridging therapy before allogeneic stem-cell transplantation. Age at diagnosis was 72 years in the newly diagnosed cohort and 58 years in the relapsed cohort, 19 (50%) patients were female, 20 (53%) patients were transfusion dependent, and bone marrow blast count was 43% (interquartile range, 26-80). Most patients (58%) had poor or very poor risk AML. Patients received a median (range) of 7 (3-13) therapy cycles. The median (range) OS in the newly diagnosed and previously treated patient groups were 308 (175-580) days and 346 (293-628) days, respectively (P = .94). Median OS in the 3 patients treated before allogeneic stem-cell transplantation has not been reached. Sixty-day mortality was 7.9%, with no difference between the 2 groups. Ongoing or increasing transfusion dependency was associated with adverse outcome (hazard ratio, 3.09; 95% confidence interval, 1.29-7.37, P = .011). Conclusion: Treatment with azacitidine led to a median OS of 10 months in both a previously untreated and a previously treated frail AML patient cohort. A positive effect in transfusion dependency was observed in 29% of these patients and was associated with better survival.

DOI: https://doi.org/10.1016/j.clml.2015.09.003

Efficacy of Azacitidine in de Novo and Relapsed Acute Myeloid Leukemia: A Retrospective Comparative Study.

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Financial support: None

Conflict of interest: None

Running title: Azacitidine in AML

Abstract

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Patients and Methods: We retrospectively analyzed all AML patients treated with azacitidine at the University Hospital Zurich and the Kantonsspital Munsterlingen between January 2005 and December 2011. Primary end-point was overall survival.

Results: Thirty-eight patients were included in the analysis. Twenty-one (55%) patients had newly diagnosed AML, 14 (37%) relapsed AML, and 3 (8%) underwent bridging therapy prior to allogeneic stem cell transplantation (SCT). Age at diagnosis was 72 years in the newly diagnosed and 58 in the relapsed cohort, 19 (50%) patients were female, 20 (53%) patients were transfusion dependent, and the bone marrow blast count was 43% (IQR 26-80). Most patients (58%) had poor or very-poor risk AML. Patients received a median of 7 (3-13) therapy cycles. The median overall-survival in the newly diagnosed and the previously treated patient groups were 308 (175-580) and 346 (293-628) days, respectively (p=0.94). Median OS in the three patients treated prior to allogeneic SCT has not been reached. 60 day mortality was 7.9% with no difference in the two groups. Ongoing or increasing transfusion dependency was associated with adverse outcome (HR 3.09; 95% CI 1.29-7.37; p=0.011).

Conclusions: Treatment with azacitidine led to a median overall survival of 10 months in both, a previously untreated and a previously treated frail AML patient cohort. A positive effect in transfusion dependency was observed in 29% of these patients and was associated with better survival.

MicroAbstract

Azacitidine is a treatment option for patients with acute myeloid leukemia (AML) who cannot tolerate intensive chemotherapy. It is still unknown which patients will benefit most from azacitidine treatment. Therefore, we conducted a retrospective comparative study on forty patients with newly diagnosed and relapsed AML. We found no significant difference in overall survival time (10 months) between these two patient groups. Prior treatment does

not predict poor outcome. Achievement of transfusion independency was associated with longer survival.

Clinical Practice Points

- Clinical response of non- intensive chemotherapy in patient with AML is unsatisfactory
- Some patients with AML do respond to treatment with hypomethylating agents such as azacitidine and decitabine. However, response to treatment cannot yet be predicted.
- A head to head efficacy analysis of azacitidine in previously treated, relapsed patients and newly diagnosed patients is lacking.
- Our data shows that treatment with azacitidine leads to a median overall survival of 10 months both in pretreated patients as well as newly diagnosed patients.
- All patients with azacitidine not undergoing allogeneic stem cell transplantation eventually died.
- Achievement of transfusion independence is associated with better outcome
- Treatment with azacitidine is associated with a relatively low early mortality rate (<10%).
- The need for hospitalization was 15 days in the newly diagnosed and 32 in the previously treated patient group, respectively (p=0.349).
- Pretreatment did not lead to an inferior outcome in our patient cohort. Better predictors for a response to hypomethylating agents in AML are needed.

Key words

Acute myeloid leukemia

Azacitidine

Transfusion

Overall survival

Hospitalization

Introduction

Acute myeloid leukemia (AML) affects 2-4/100000 persons annually resulting in approximately 160 to 320 new diagnoses in Switzerland per year.[1] AML has an increasing incidence by age.[2] A substantial fraction of younger AML patients can be cured with intensive chemotherapy, and indeed, data from the Swedish Acute Leukemia Registry have shown that outcome is also improved in elderly patients undergoing intensive chemotherapy compared to other treatment options; nevertheless the majority of patients will not undergo intensive chemotherapy for various reasons, particularly due to higher therapy associated morbidity and mortality as well as overall decreased response rates.[3-5] In patients not treated with intensive chemotherapy, low-dose cytarabine is superior to best supportive care and has long been considered the standard of care for these patients.[6] However, in recent years novel drugs such as the epigenetic modifiers azacitidine and decitabine have emerged as treatment options for patients with hematologic malignancies. Azacitidine and decitabine are nucleoside analogues of cytidine. Their antineoplastic effect seems to be related to DNA hypomethylation.[7] Azacitidine has been shown to lead to a statistically significant increase in life-expectancy in patients with high-risk myelodysplastic syndromes (MDS) as well as in patients with AML with myelodysplasia-related changes and a low blast count of 20-30%. [8,9] As a consequence, these results raised interest in using azacitidine and decitabine in AML patients with bone marrow blast counts of 30% and more. In our institutions we started to study the off-label use of azacitidine in selected AML patients unfit for intensive chemotherapy in 2005.

Patients and Methods

Patients and clinical data

Patients 18 years of age or older with a confirmed diagnosis of AML according to the WHO 2008 criteria and a blast count of ≥20% were eligible if they received at least one cycle of azacitidine. Patients received azacitidine either because they chose not to undergo intensive therapy, or because they were considered unfit for intensive chemotherapy by their treating physicians based on their age, performance status, comorbidities or unlikely to achieve lasting remissions upon intensive chemotherapy due to disease biology as determined by cytogenetics.[10] Azacitidine was considered the treatment of choice in patients with early relapse after intensive chemotherapy (< 6 months), and no available allogeneic stem cell donor. Both newly diagnosed as well as pretreated patients were included. However, patients participating in the SAKK 30/07 trial were excluded from the analysis, and have been reported elsewhere.[11] Patient inclusion lasted from January 1st, 2005 to December 31st, 2011. End of follow-up was June 30th, 2014. Clinical information was extracted from patient's charts. The retrospective study was approved by the local ethical committees of the Kanton Zurich and Kanton Thurgau, Switzerland (KEK-ZH-Nr.2012-0402).

Treatment regimes

Treatment with azacitidine could be administered subcutaneously at a dose of 100mg/m^2 for five consecutive days or at a dose of 75mg/m^2 for 7 consecutive days of a 28 day cycle. Most outpatients were treated according to the 5-days schedule. No standard anti-infectious prophylaxis was employed. The choice of supportive care, including the transfusion policy was left to the treating physicians' discretion.

End points

Primary end-point was overall survival. Secondary end-points were 60 day mortality, hospitalisation days, transfusion dependency, response to azacitidine, median number of treatment cycles, and azacitidine side effects.[12]

Statistical Analysis

We calculated descriptive statistics. Data were reported as proportions, and medians with interquartile ranges (IQR). Data were presented separately for the subgroup of patients with newly diagnosed AML, previously treated AML and Patients who underwent bridging therapy prior to allogeneic stem cell transplantation. Patient characteristics among groups were compared by non-parametric tests as appropriate. Survival after initiation of azacitidine treatment was estimated by the Kaplan-Meier method and log-rank test was used to compare survival curves. Univariate cox regression analysis was applied to investigate potential associations between survival and patient characteristics such as transfusion dependency, performance status (ALMA score) and AML risk score

Results

Patient characteristics

Forty patients were screened, two had to be excluded due to incomplete follow-up data, and thirty-eight were included in the analysis. Twenty-one (55%) patients had newly diagnosed AML, 14 (37%) AML relapse, and 3 (8%) underwent bridging therapy prior to allogeneic stem cell transplantation. The median age at diagnosis was 67 years. Newly diagnosed patients were significantly older than patients with relapsed AML (median 72.2 years (IQR 67.6 – 77.2) vs. 58.1 years (IQR 51.9-64.9); p=0.001). Nineteen (50%) patients were female, 20 (53%) patients were transfusion dependent and the median bone marrow blast count at diagnosis was 43% (interquartile range 26-80). More than half of the patients (58%) had poor or very-poor risk AML according to the HOVON/SAKK 102 risk stratification. The European ALMA score was 2 (IQR 1-3) for all treatment groups.

Patients were then further stratified in a newly diagnosed group, a previously treated group and patients with bridging therapy prior to allogeneic stem cell transplantation (Table 1). The main reasons for azacitidine treatment in the newly diagnosed patients were age (median age 78.3 years, IQR 76.7-79.3) (38%), ECOG ≥2 and/or significant co-morbidities (29%), followed by unfavorable caryotype (14%) and patient choice (14%). Time to azacitidine

treatment was significantly shorter in the newly-diagnosed group as they did not undergo prior AML treatment (median 10.5 days (IQR 7-31) vs. 247 days (IQR 142-417); p=0.001). Seventy-one percent in the newly diagnosed and 30% in the relapsed AML patients needed blood transfusions during the 30 days prior to azacitidine treatment (p=0.036). The bone marrow blast count was 40% in the newly diagnosed, and 32.5% in the relapsed patients (p=0.11). The median number of azacitidine cycles was 7 and 7.5, respectively (Table 2)

Survival

The median overall survival (OS) after initiation of azacitidine therapy did not differ significantly between the newly diagnosed and the previously treated patient group with 308 (175-580), and 346 (293-628), respectively (p=0.94). Median OS in the three patients with bridging therapy prior to allogeneic stem cell transplantation was not reached.
As of June 30th 2014, two and a half years after inclusion of the last patient, only two patients were still alive. Patient one with good-risk AML (AML with mutated NPM1A) went into complete remission after intensive induction chemotherapy but suffered from severe complications. He then had one cycle of azacitidine bridging prior to allogeneic hematopoietic stem-cell transplantation (HSCT). Patient two had an early molecular relapse of a good-risk AML (AML with mutated NPM1A) after induction and consolidation therapy. He was given one azacitidine bridging cycle prior to allogeneic HSCT.

Transfusion dependency and response to therapy

A decrease in the transfusion dependency was seen in 43% of the patients with newly diagnosed AML and 12% of the patients in the pre-treated AML group (Table 2). Follow-up bone marrow biopsies were performed in nine out of 21 patients (43%) with newly diagnosed AML, ten out of 14 patients (71%) with previously treated AML, and all three patients with a bridging therapy. In the newly diagnosed and the previously treated patient group three (14%), and two (14%) patients showed complete remission, three (14%), and two (14%) partial remission, three (14%), and four (29%) stable disease, respectively. Two (14%) patients in the previously treated group had primary disease progression. All three patients with a bridging therapy had ongoing complete remission.

Sixty day mortality and hospitalisation days

Three patients (7.9%) died during the first 60 days of azacitidine treatment. Total hospitalization duration including the days from diagnosis to treatment start was 15 (IQR 6-30), and 32 (IQR 9-49) days in the previously untreated and the pretreated patients group, respectively. This accounts for 4.8% and 9.2% of the median overall survival time in these patient groups.

Side effects

One patient died of pneumonitis, and even though several reasons such as heart failure, infectious complications and a preexisting lung disease might have contributed to this fatal event, a toxic side effect of azacitidine cannot be ruled out completely. No other severe unexpected side effects were noted. Due to the lack of a comparator, myelotoxicity could not be evaluated.

Survival risk factors

On univariate analysis ongoing or increasing transfusions dependency (Hazard ratio (HR) 3.09, 95% confidence interval (CI) 1.29-7.37, p = 0.011), as well as an ECOG of 3 or higher (n=3) when compared to ECOG ≤1 (n=18) (HR 4.5, 95% CI 1.32-15.18, p=0.016) were significantly associated with increased mortality. European ALMA score (HR 1.5, 95% CI 0.94-2.42, p=0.088), as well as European ALMA risk groups (p=0.093) were not predictive of overall survival, neither were the SAKK/HOVON defined poor and very poor-risk AML categories (HR 1.5, 95% CI 0.69-3.15, p=0.319), the leukocyte count at diagnosis (HR 1.0, 95% CI 0.99-1.0, p=0.208), the age at diagnosis (HR 0.99, 95% CI 0.96-1.04, p=0.932) and the blast count at the start of azacitidine treatment (HR 1.01, 95% CI 1.0-1.02, p=0.069).

Discussion and Conclusion

We here report real-world long-term follow-up data from patients with acute myeloid leukemia (AML) treated with azacitidine. Median overall survival in both, the previously untreated as well as the previously treated patient group was 10 months. The patients had to be hospitalized during 4.8% and 9.2% of the median overall survival time, which is less than reported elsewhere.[13] Early mortality within the first sixty days was low (7.9%). However, treatment with azacitidine is not curative. All patients who did not undergo subsequent allogeneic hematopoietic stem cell transplantation eventually died.

. We believe, that the lack of a difference in overall survival between the previously treated and the previously untreated patient group can mainly be explained by a counterbalance of risk factors. The patients with the supposedly more favorable newly diagnosed AML were significantly older, while relapsed patients had previously been exposed to intensive chemotherapy and were more likely to be transfusion dependent. The median overall survival time in both our patient groups is comparable to what has been recently reported. [14-18] Interestingly, decitabine has shown comparable results in AML patients, but a head-to-head comparison is lacking. [19] Hence, both decitabine and azacitidine seem to be effective and associated with low toxicity, but are only slightly superior to low-dose cytarabine, if superior at all.[18,19]

A key question is which AML patients should receive and will profit most from hypomethylating agents (HMA)? In our patient cohort, achieving transfusion independency was clearly associated with better overall survival. Hence, we do know, that hematologic responders do better than non- responders.[20] But earlier predictors of an HMA treatment response are warranted. As for now, no large randomized trials included comprehensive biomarker analysis to better understand potential markers predictive of treatment response.[18] Meanwhile, in an attempt to use clinical information to predict treatment outcome, the so-called European ALMA score has been proposed for patients with AML.[14] It identifies three patient subsets with different overall survival and HMA treatment responses based on the initial white blood cell count, ECOG and cytogenetic abnormalities. However, we were not able to reproduce these data in our patient cohort which might be explained by differences in sample size as well as patient characteristics, as we included pretreated and not only newly diagnosed patients in our analysis. Patients with an ECOG of 3 or higher showed increased mortality, but the number of patients in our study was small (n=3).

Our retrospective study does have limitations as we only report the results of a relatively small and heterogeneous patient population, who has been judged to be unfit for intensive chemotherapy by their treating physicians and not by a clearly defined study protocol. Nevertheless, our real-world data might add information and insights to better counsel patients on what can be expected from a treatment with azacitidine.

Table 1: Baseline characteristics of patients

	newly diagnosed AML n= 21	previously treated AML n = 14	Bridging to allogeneic SCT n=3	
age[§]	72.2 (67.6 – 77.2)	58.1 (51.9-64.9)	59.6 (57.8-66.2)	p=0.001
sex (%)				p=1.0
- male	10 (47)	7 (50)	2 (67)	
- female	11 (53)	7 (50)	1 (33)	
ECOG	1 (1-2)	1.5 (1-2)	2 (1-3)	p=0.676
diagnosis[#] (%)				
- AML NOS	7 (33)	3 (21)	1 (33)	p=0.177
- AML with mutated NPM1A	1 (5)	3 (21)	2 (67)	
- AML with myelodysplasia-related changes	7 (33)	7 (50)	0	
- therapy-related AML	4 (19)	1 (7)	0	
- myeloid sarcoma	2 (10)	0	0	
AML risk at diagnosis[&] (%)				p=0.111
- good	1 (5)	2 (14)	2 (67)	
- intermediate	7 (33)	1 (7)	1 (33)	
- poor	8 (38)	8 (57)	0	
- very poor	4 (19)	2 (14)	0	
- not known	1 (5)	1 (7)	0	
bone marrow blast count[§]				
- diagnosis	40 (28-83)	42.5 (25-68.8)	30 (5-80)	p=0.722
- start of azacitidine treatment	40 (28-83)	32.5 (8.8-56.3)	5 (5-5)	p=0.012
leukocyte count[§]				
- diagnosis	7.1 (1.7-19.8)	3 (2-36.7)	3.2 (2.4-20.7)	p=0.982
transfusion dependence[+]				
- platelet	4 (19)	0	0	p=0.127
- red blood cells	9 (43)	3 (18)	0	
- platelets and red blood cells	2 (9)	2 (12)	0	
- none	6 (29)	9 (70)	3 (100)	
prior therapy				
- induction chemotherapy	na	13 (94)	3 (100)	
- allogeneic stem cell transplantation	na	1 (6)	0	
European ALMA Score (IQR)[14]	2 (1-3)	2 (1-3)	2 (1-3)	p=0.935
Days to azacitidine treatment from primary diagnosis[§]	10.5 (7-31)	247 (142-417)	84 (65-477)	p=0.001

[§] median (IQR), [#] according the WHO 2008 classification, [&] according the SAKK102/HOVON study protocol, [+] one month prior to azacitidine treatment

Table 2: Outcome analysis

	Newly diagnosed AML (n = 21)	Previously treated AML (n=14)	Bridging to allogeneic SCT (n=3)	
therapy cycles[§]	7 (3-13)	7.5 (5.8-12.8)	1 (1-3)	p=0.037
overall survival (days) [§+]	308 (175-580)	346 (293-628)	min. 787; max. 1210 (=end of follow up)	p=0.022
60 day mortality, N (%)	2 (9.5)	1 (7.1)	0 (0)	p=1.0
hospitalization (days) [§]	15 (6-30)	32 (9-49)	21 (0-61)	p=0.349
transfusion dependency (%) - stable - decrease - increase - not known	 4 (19) 9 (43) 7 (33) 1 (5)	 3 (22) 2 (14) 9 (64) 0	 3 (100) 0 0 0	p=0.030

[§] median (IQR), [+] following day one of the azacitidine treatment

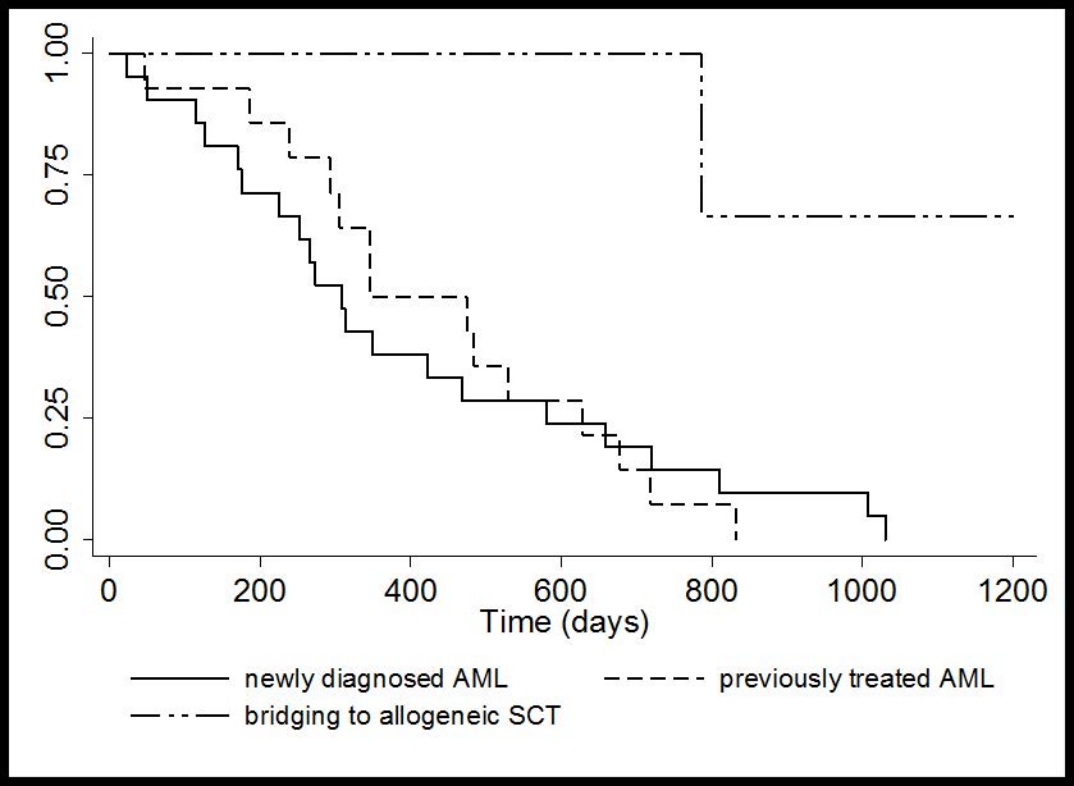
Figure 1: Overall survival after initiation of azacitidine treatment.

The median overall survival after azacitidine initiation was 308 days (IQR 175-580; min. 22, max. 1031) days in the newly diagnosed, and 346 (IQR 293-628; min. 46 max. 832) days in the previously treated patient group (p=0.94). One patient in the previously treated group, who had bridging therapy prior to allogeneic stem cell transplantation died after 787 days, the other two patients with bridging therapy prior to allogeneic stem cell transplantation were still alive at end of follow up (1210 days).

References

1. Rodriguez-Abreu D, Bordoni A, Zucca E. Epidemiology of hematological malignancies. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 2007;18 Suppl 1:i3-i8.
2. Juliusson G, Lazarevic V, Horstedt AS, Hagberg O, Hoglund M, Swedish Acute Leukemia Registry G. Acute myeloid leukemia in the real world: why population-based registries are needed. Blood 2012;119:3890-9.
3. Juliusson G, Antunovic P, Derolf A, et al. Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish Acute Leukemia Registry. Blood 2009;113:4179-87.
4. Juliusson G, Swedish AMLG. Most 70- to 79-year-old patients with acute myeloid leukemia do benefit from intensive treatment. Blood 2011;117:3473-4.
5. Burnett A, Wetzler M, Lowenberg B. Therapeutic advances in acute myeloid leukemia. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2011;29:487-94.
6. Burnett AK, Milligan D, Prentice AG, et al. A comparison of low-dose cytarabine and hydroxyurea with or without all-trans retinoic acid for acute myeloid leukemia and high-risk myelodysplastic syndrome in patients not considered fit for intensive treatment. Cancer 2007;109:1114-24.
7. Muller AM, Florek M. 5-Azacytidine/5-Azacitidine. Recent results in cancer research Fortschritte der Krebsforschung Progres dans les recherches sur le cancer 2014;201:299-324.
8. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. The Lancet Oncology 2009;10:223-32.
9. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2010;28:562-9.
10. Kantarjian H, Ravandi F, O'Brien S, et al. Intensive chemotherapy does not benefit most older patients (age 70 years or older) with acute myeloid leukemia. Blood 2010;116:4422-9.
11. Passweg JR, Pabst T, Blum S, et al. Azacytidine for acute myeloid leukemia in elderly or frail patients: a phase II trial (SAKK 30/07). Leukemia & lymphoma 2014;55:87-91.
12. Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 2006;108:419-25.
13. Lao Z, Yiu R, Wong GC, Ho A. Treatment of elderly patients with acute myeloid leukemia with azacitidine results in fewer hospitalization days and infective complications but similar survival compared with intensive chemotherapy. Asia-Pacific journal of clinical oncology 2015;11:54-61.
14. Ramos F, Thepot S, Pleyer L, et al. Azacitidine frontline therapy for unfit acute myeloid leukemia patients: clinical use and outcome prediction. Leukemia research 2015;39:296-306.
15. Thepot S, Itzykson R, Seegers V, et al. Azacitidine in untreated acute myeloid leukemia: a report on 149 patients. American journal of hematology 2014;89:410-6.
16. Pleyer L, Burgstaller S, Girschikofsky M, et al. Azacitidine in 302 patients with WHO-defined acute myeloid leukemia: results from the Austrian Azacitidine Registry of the AGMT-Study Group. Annals of hematology 2014;93:1825-38.
17. Itzykson R, Thepot S, Berthon C, et al. Azacitidine for the treatment of relapsed and refractory AML in older patients. Leukemia research 2015;39:124-30.
18. Dombret H, Seymour JF, Butrym A, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. Blood 2015.
19. Kantarjian HM, Thomas XG, Dmoszynska A, et al. Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-

dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2012;30:2670-7.
20. Sadashiv SK, Hilton C, Khan C, et al. Efficacy and tolerability of treatment with azacitidine for 5 days in elderly patients with acute myeloid leukemia. Cancer medicine 2014;3:1570-8.


1.00
0.75
0.50
0.25
0.00
0
200
400
600
800
1000
1200
Time (days)
newly diagnosed AML
previously treated AML
bridging to allogeneic SCT